AD_____

AWARD NUMBER: W81XWH-04-1-0490

TITLE: Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaska

PRINCIPAL INVESTIGATOR: Caroline M. Tanner, M.D., Ph.D.

CONTRACTING ORGANIZATION: Parkinson's Institute
Sunnyvale, California 94089-1605

REPORT DATE: May 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Caroline M. Tanner, M.D., Ph.D.

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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Parkinson's Institute
Sunnyvale, California 94089-1605

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14. ABSTRACT

The intent of this research is to conduct a case control study of Parkinson's Disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determine by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project will be conducted in two phases. Phase 1 is a developmental period and is currently ongoing. During this time, the specific aspects of the study design are being established, detailed protocols are being developed, and the necessary approvals for the research are being obtained. Once Phase 1 is complete, Phase 2 will be initiated. During Phase 2 the study will be conducted.

15. SUBJECT TERMS
Parkinson's disease, polychlorinated biphenyl, organochlorine pesticides, methylmercury, Alaska natives, neurodegeneration

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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A. Introduction

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Native people to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides, and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interviews, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project will be conducted in two phases. Phase 1 is a developmental period and is currently ongoing. During this time, the specific aspects of the study design are being established, detailed protocols are being developed, and the necessary Institutional Review Board (IRB) approvals for the research are being obtained. During Phase 2 the study will be conducted. Phase 2 will be initiated following completion of Phase 1.

B. Body

SCOPE OF WORK - PHASE 1

Task 1: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.
Task 2: Develop methods for identifying matched controls.
Accomplishments:
Since the last reporting period, study personnel traveled to AK 2 times to meet with collaborating neurologists and representatives of the AK Area Institutional Review Board (IRB) to refine case and control ascertainment methods.

Task 3: Develop a preliminary proposal for review by Alaska Native leaders. Subsequent detailed versions of the study protocol will be submitted for review in accordance with protocol.
Accomplishments:
To date, the study protocol, data collection instruments, and informed consents were submitted and approved by all necessary regulatory boards for study conduct in Anchorage (Alaska Area IRB, SouthCentral Foundation (SCF), Alaska Native Tribal Health Consortium (ANTHC), Western Institutional Review Board (WIRB), VA Pacific Islands Health Care System, and University of CA San Francisco (UCSF) Committee on Human Research.) In February 2006, the study protocol, data collection instruments, and informed consents were submitted to the Army for review. On March 5, 2007, we received a Memorandum For Record (MFR) requesting changes to the protocol and consents. Revisions were submitted, and final approval of the revisions is pending. Once approval is received by the Army, we will submit revised documents to each of the boards listed in Table 1.

Task 4: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager, and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.

Accomplishments:
We recently hired (April 2007) an Alaska based study coordinator, Amy Wiita. We are engaging in study preparation and training activities with her so that recruitment activities can begin immediately after receiving all study approvals.

Dr. Gordon, one of the 2 neurologists and collaborators on this project, passed away early in 2007. Dr. Trimble will assume his study responsibilities, including ascertainment and neurologic evaluations of cases, when study enrollment begins.

Task 5: Develop study instruments and a detailed protocol.
Accomplishments:
This was completed during year 2. We developed a study protocol and study instruments for collecting detailed life histories with special focus on exposures through diet, place of residence, and occupational exposures. However, the study protocol and instruments have been under review by the Army since February 2006. Piloting of the questionnaires within the Alaska Native population cannot proceed until we receive approval from the Army and other institutions involved in the research. When approval from the Army is received, we will need to resubmit to our group of collaborating institutions based on revisions requested by the Army.

Task 6: Refining the study protocol and preparing the operations manual.
Accomplishments:
Per the Army's request, the IRB approved study protocol was revised. The revisions are currently under review by the Army. When final approval of the protocol and instruments is obtained, any appropriate changes will be made to the operations manual.

Task 7: IRB approval of final protocols.
Accomplishments:
This continues to be a challenging and rigorous task. There have been many unexpected delays in achieving approval to conduct this work in a native population. Final IRB approval is still pending (see Table 1). To date, we received approval from all necessary IRBs. However, following those approvals, the Army requested changes to the protocol and consent forms. We have submitted these revised documents to the Army and are awaiting approval. As soon as the Army approves all study documents, we will resubmit any revised documents to all IRBs prior to initiating piloting or enrollment into the study.

Upon approval by all of the above, we will submit all certificates of approval to the US Army Office of Research Protections. After their review and approval, we will be allowed to recruit subjects at the ANMC. As the study expands to other regions of Alaska, we will seek approval by Native Health Corporations in those regions. Submissions to regional corporations are currently being prepared.

Table 1. Human Subject Approval Status

Institution	Review Board	Status	Approval Date	Expiration Date
Parkinson's Institute	WIRB	Approved	7/31/2006	7/31/2007
ANMC	AK Area IRB	Approved	1/31/2006	11/7/2007
ANMC	ANTHC - Board of Directors	Approved	6/14/2006	NA
ANMC	SCF	Approved	4/11/2006	NA
AK Statewide (Outside Anchorage basin)	Native Corporations as necessary	not submitted		
PHRI	VA Pacific Islands Health Care System	Approved	11/7/2006	11/6/2007
UCSF	UCSF Committee on Human Research	Approved	9/7/2004	9/7/2007
US Army	Office of Research Protections (Army)	Submitted	pending	

ANMC	Alaska Native Medical Center
PHRI	Pacific Health Research Institute
UCSF	University of California San Francisco
WIRB	Western Institutional Review Board
ANTHC AMP RC	Alaska Native Tribal Health Consortium Abstracts, Manuscripts and Proposals Review Committee
SCF	SouthCentral Foundation

SCOPE OF WORK - PHASE 2

Initiation of phase 2, the conduct of the study, is pending final approval from the Army and approval of Army requested revisions by the review boards listed in Table 1.

C. Key Research Accomplishments

- Met with collaborating neurologists in AK and other local investigators to develop potential methods of case and control ascertainment.
- Extensive meetings with Alaska review board representatives to satisfy the requests of board members.
- Revisions to study instruments, consents, and protocols to make them more culturally appropriate and satisfy the requests of the many reviewers.
- Human subjects approval was obtained by all of the required review boards (see Table 1).
- Responded to the Army regarding revisions to study documents.

D. Reportable Outcomes

While many milestones of phase 1 of this study were met, we are still in the process of obtaining approvals necessary to begin study conduct. Until this has been accomplished and study conduct finished, we will not have reportable outcomes.

E. Conclusions

Phase 1 of this study is well underway. We anticipate having the appropriate IRB approvals and beginning study conduct (Phase 2) by summer 2007. Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions.

F. References

None

G. Appendices

Copies of current human subject approvals are enclosed:

- WIRB
- AK Area IRB
- SCF
- ANTHC
- UCSF
- PHRI

WIRB®
(360) 252-2500
1-800-562-4789
FAX: (360) 252-2498

Western Institutional Review Board ®

Western International Review Board®

3535 SEVENTH AVENUE, SW, OLYMPIA, WA 98502-5010
P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Caroline M. Tanner M.D., Ph.D.
1170 Morse Avenue
Sunnyvale, California 94089-1605

BOARD ACTION DATED: 07/31/2006
PANEL: 7
STUDY APPROVAL EXPIRES: 07/31/2007
STUDY NUM: 1060268
WIRB PRO NUM: 20041208
INVEST NUM: 8644
WO NUM: 1-379211-1

SPONSOR: US Army Medical Research Acquisitions Activity
PROTOCOL NUM: W23RYX-4007-N601
AMD. PRO. NUM:
TITLE:
Polychlorinated Biphenyls, Organochiorines and Parkinson's Disease Risk A Case Control Study in Alaska Natives

APPROVAL INCLUDES:

Investigator
Protocol (06-29-2006)
Medical Records Release Authorization #3561426.0 - Legal Representative - As Submitted
Medical Records Release Authorization #3561442.0 - As Submitted

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Association for the Accreditation of Human Research Protection Programs, Inc. — Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

8/3/2006
(Date)

This document electronically reviewed and approved by Schultz, Ted on 8/3/2006 9:10:50AM PST. For more information call Client Services at 1-360-252-2500

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.

    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB.

    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

3. Obtain pre-approval from WIRB for any planned deviations that could adversely affect the safety or welfare of subjects, or the integrity of the research data and any changes in the research activity. The only exception is when changes are necessary to eliminate apparent immediate hazards to subjects. Immediately report to WIRB any such emergency changes implemented.

4. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial.

    a. Report to WIRB all adverse events that are serious, unexpected and related, within 10 days of the investigator becoming aware of them. Other unexpected adverse events that involve risks to study subjects or others are to be submitted with continuing review reports.

    b. Promptly report to WIRB other unanticipated problems involving risks to human subjects or others. These events do not readily fit the formal definition of Adverse Event, but could impact human subject safety and/or rights. Examples include theft of a computer containing private identifiable subject information, or study staff getting ill from inhaling a study agent.

    c. Provide reports to WIRB concerning the progress of the research, when requested.

5. Report to WIRB any unplanned protocol variance that could adversely affect the safety or welfare of subjects, or the integrity of the research data, within 10 days of becoming aware of the variance. Other unplanned variances may be recorded on a log and submitted with continuing review reports.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

DISTRIBUTION OF COPIES:

Contact	**Company Name**
Caroline M. Tanner M.D., Ph.D.	The Parkinson's Institute
Monica Korell	The Parkinson's Institute

SITES: If the PI has an obligation to use another IRB for any site listed below and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

Address
1170 Morse Avenue, Sunnyvale, California 94089-1605

Southcentral Foundation

April 11, 2006

Caroline M. Tanner, MD, PhD, Director of Clinical Research
The Parkinson's Institute
1170 Morse Ave.
Sunnyvale, CA 94089

Dear Dr. Tanner:

The proposal entitled "Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Native People" was reviewed by the Southcentral Foundation (SCF) Board of Directors on April 11, 2006.

We have approved this proposal with the understanding that you will abide by the standard stipulations outlined in the enclosed Research Agreement. Please sign and return it to me at your earliest convenience.

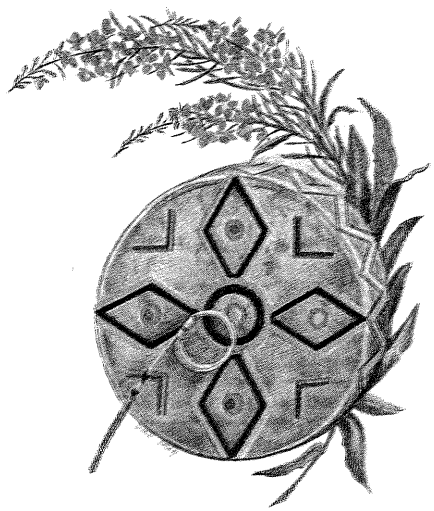
This research project may begin as soon as SCF receives the signed Research Agreement from you. If you have any questions about these stipulations, please contact me at 729-5471.

Sincerely yours,

SOUTHCENTRAL FOUNDATION

Ruth A Etzel

Ruth A. Etzel, M.D., Ph.D.
Medical Director Research



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DEPARTMENT OF VETERANS AFFAIRS
VA PACIFIC ISLANDS HEALTH CARE SYSTEM
Spark M. Matsunaga Medical Center
459 Patterson Road
Honolulu HI 96819-1522

November 7, 2006

In Reply Refer To: 151

G. Webster Ross, MD
VAPIHCS
459 Patterson Road
Honolulu, HI 96819-1522

Subject: Research Proposal Title: "Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska natives - VAPIHCS Protocol" 2006-01/GWR/PROMISE 0013

Dear Dr. Ross:

I am pleased to inform you that on November 7, 2006 the VAMC Research & Development Committee (RDC) reviewed and unanimously approved your project for a one year period. The RDC concurred with the IRB evaluation and level of human subject risk of "minimal risk" for this study and the IRB's approval of human subject use for a period of one-year.

Your Annual Project Update must be completed prior to November 6, 2007. The Annual Update must be filed with the R&D Office at least one month prior to the October 2007 meeting.

The R&D Committee is normally held on the first Tuesday of each month; however, the schedule can change depending on availability of members. Please check with the R&D Office in advance for the final schedule.

If you have any questions, please contact Douglas Miller, Research Committee Coordinator at (808) 433-0127 or e-mail: douglas.milller@med.va.gov.

Sincerely,

James P. Epure, MD
Chairperson, R&D Committee

Committee on Human Research

Project Summary Sheet

CHR: H6442-25720-03

Study Title

Polychlorinated Biphenlys, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Natives

Principal Investigator

Marion M. Lee Title: Professor

Department: Epidemiology & Biostatistics

Phone: 514-8117 Fax: E-Mail: marion.lee@ucsf.edu

Address: Box 0981

Contacts

Name	Position	Box	Phone	E-Mail
Etkin, Coral	Former Contact	0560	476-8945	cetkin@epi.ucsf.edu
Lee, Marion M.	PI	0981	514-8117	marion.lee@ucsf.edu

Human Subjects Training

The PI and Co-PI must complete the UCSF online training course: Protecting Human Research Subjects

Name	Last Completed
Lee, Marion M.	9/16/04

Review Details

Approval Number	Status	Received	Reviewed	Approved	Expires
H6442-25720-03	Approved	8/17/2006 10	8/30/2006 12:	8/30/2006 12	9/7/2007 12
H6442-25720-02	Approved	8/5/2005 12:(	8/26/2005 12:	8/26/2005 12	9/7/2006 12
H6442-25720-01	Approved	8/19/2004 12	9/7/2004 12:0	9/7/2004 12:(	9/7/2005 12

Attachments:

Special Study Information

Site: Campus
Other

Populations:

How many subjects will be enrolled here: 200

Will subjects be paid: Yes

Drugs and Devices

Name	IND/IDE No.

Funding

Agency / Sponsor Name	Award No.	Type	Funded
DOD			Yes

FederalWide Assurances

The CHR is the Institutional Review Board (IRB) for UCSF and its affiliates. The institutional FederalWide Assurance (FWA) numbers are listed below. Not all of the following FWA numbers apply to this study.

Institution	FWA #
UCSF	00000068
Ernst Gallo Clinical and Research Center (EGCRC)	00000304
J. David Gladstone Foundation	00000087
Northern California Institute for Research and Education (NCIRE)	00000256
San Francisco department of Public Health (SFDPH)	00000162
San Francisco General Hospital (SFGH)	00000315
Veterans Affairs Medical Center (VAMC)	00000280

University of California, San Francisco
Office of Environmental Health and Safety
Box 0942

December 8, 2006

Caroline Tanner, MD, PhD
The Parkinson's Institute
1170 Morse Avenue
Sunnyvale, CA 94089

Dear Dr. Tanner and Dr. Trimble:
Thank you for submitting the Status Report and Renewal Application Report to the Alaska Area Institutional Review Board (AAIRB) for the protocol **2005-04-005 Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Natives**. During the November 7, 2006 meeting of the AAIRB the protocol and consent forms were reviewed and approved by the AAIRB. This approval is valid until November 7, 2007.

Prior to making any changes to the consent form or protocol you must receive approval from the Alaska Area IRB. Please request our annual renewal forms from the AAIRB Administrator at least 6 weeks prior to the protocol expiration date. Please ensure that project renewal information is complete and submitted to the AAIRB Administrator at least four weeks prior to expiration. The annual renewal information should include but not be limited to the Alaska Area IRB annual renewal form, a current copy of the consent/assent forms, a cover letter to the IRB with a project summary and an electronic copy of all items to be sent to the IRB members. The submission date for the monthly IRB meeting is the first day of each month. Inform the IRB by letter when the protocol is complete/closed.

As a reminder, the IRB must review and approve all human subjects research protocols at intervals appropriate to the degree of risk, but not less than once per year. Per 45 CFR 46.109(e), there is no grace period beyond one year from the last IRB approval date unless the protocol approval period is shorter than one year. It is your responsibility as Principal Investigator (PI) to maintain approval status for your project by tracking, renewing and obtaining IRB approval for all modifications to the protocol and the consent form. Keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. To avoid lapses in approval of your research which will result in suspension of participant enrollment and/or termination of the protocol submit the protocol continuation request at least 4 weeks prior to **expiration date of November 7, 2007.**

All research approved by the Alaska Area IRB is subject to 45 CFR 46 "Protection of Human Subjects" regulations and the principles of the Belmont Report. Investigators are expected to be familiar with these provisions and adhere strictly to all requirements. You are required to have all personnel involved in the research complete the training at www.citiprogram.org every 36 months. Please retain your completion certificates from the Collaborative IRB Training Institute (CITI).

Renewal forms may be obtained from the IRB Administrator. Please ensure that renewal information is received by the AAIRB Administrator at least six weeks prior to expiration. As a reminder the AAIRB must review and approve all human subjects research protocols at intervals appropriate to the degree of risk, but not less than once per year. Per 45 CFR 46.109(e) there is no

grace period beyond one year from the last AAIRB approval date. It is ultimately the responsibility of the Principal Investigator (PI) to submit the research protocol for continuation, review and approval by the AAIRB. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. To avoid lapses in approval of your research and the possible suspension of participant enrollment and/or termination of the protocol submit the Status Report and Renewal Request form at least six weeks prior to the expiration date of November 7, 2007.

Please note that storage and use of all biological materials collected from or derived from research participants must conform to the Alaska Area Specimen Banking protocol. This includes clinical material which may be stored in clinical laboratories.

After Alaska Area IRB approval is obtained, all research involving staff, patients, or resources at the Alaska Native Medical Center (ANMC) must be submitted to the Board(s) of Directors of ANMC's parent organizations - Southcentral Foundation and the Alaska Native Tribal Health Consortium. Your point of contact at the Southcentral Foundation is:

Dr. Ruth Etzel: raetzel@soucentralfoundation.com

For the Alaska Native Tribal Health Consortium, the contact is:

Dr. Anne Lanier: aplanier@anthc.org

Please send your proposal and a copy of the IRB approval letter to both. All research protocols must receive Tribal approval and clearance after Alaska Area Institutional Review Board review.

Before submitting any manuscripts, reports, or abstracts for consideration for publication or presentation, Board of Directors review must be obtained. To ensure timely review, please send an electronic copy of these items to both Dr. Etzel and Dr. Lanier at least 8 weeks before the deadline for submission.

Please feel free to contact me with questions related to the Alaska Area Institutional Review Board. My contacts are tjpowell@anmc.org or call (907) 729-3924 between the hours of 8:00am and 4:00pm, Monday through Friday.

Sincerely,

Terry J. M. Powell
IRB Administrator
Alaska Area Institutional Review Board

Cortese, Katey

To: Cortese, Katey

Subject: FW: UPDATE: proposal status

From: Ferucci, Elizabeth D [mailto:EDFerucci@anmc.org]
Sent: Wednesday, June 14, 2006 3:59 PM
To: Korell, Monica
Cc: Lanier, Anne P; Etzel, Ruth A
Subject: UPDATE: proposal status

Dear Monica:

The proposal entitled "Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Natives" was approved today by the ANTHC Board of Directors. This completes the ANTHC approval process.

Dr. Ruth Etzel can provide information regarding timing of SCF review, if that has not completed yet.

Thanks,

Liz

Elizabeth D. Ferucci, MD
Medical Research Associate
Office of Alaska Native Health Research
Alaska Native Tribal Health Consortium
Phone 907-729-4591
Fax 907-729-2924
edferucci@anmc.org